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TIME-RELATED FACTORS IN RESEARCH ON DIET AND CANCER

DEMETRIUS ALBANES, ARTHUR SCHATZKIN and MARC S. MICOZZI

Cancer Prevention Studies Branch, Prevention Program, Division of Cancer Prevention and Control, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, U.S.A.

Abstract—Time-related factors have been an integral aspect of laboratory and epidemiologic studies concerning the effects of diet on cancer. In this survey, we illustrate several ways in which consideration of time factors has furthered our understanding in this area. As one of the key dimensions in descriptive studies of secular trends and migrant populations, time factors suggest general associations between diet and cancer. The investigation of time-related parameters such as age, duration of dietary exposure, and time from exposure to cancer, lends greater specificity to the diet–cancer relationship. Both micro- and macro-nutrients are examined, as well as nutrition-mediated factors such as growth and anthropometry. Time-related issues relevant to the design of future observational and intervention studies of diet and cancer (i.e. critical etiologic periods, timing of dietary assessment, biological indicators, and secular trends) are also discussed.

Anthropometry Cancer Diet Epidemiology Nutrition Time

INTRODUCTION

Research on diet and cancer has become an important scientific focus in recent years [1], although the view of diet as an etiologic factor in human carcinogenesis is not new [2]. The role played in the development of cancer by dietary macronutrients such as fats, fiber, and total calories, as well as by several vitamins (e.g. A, C, and E) and minerals (e.g. selenium) is under intense investigation. Time-related factors have been an important aspect of both laboratory and epidemiologic studies in this area. As one of the key dimensions in descriptive studies, time factors (along with person and place) have suggested *general* relationships between dietary factors and cancer. The investigation of time-related factors such as age, duration of dietary exposure, and time from exposure to cancer outcome, lends greater specificity to the diet–cancer relationship. A broad and, necessarily, schematic overview of these issues is presented, drawing examples from the available literature. In addition, the relevance of such time considerations to the design of epidemiologic studies and cancer chemoprevention trials is examined.

TEMPORAL ASPECTS IN DIET–CANCER RESEARCH

The diet–cancer relation has been explored in a number of descriptive studies that examine secular trends, international correlations and migrant populations. While these studies have contributed to our current understanding by providing evidence for general associations between diet and cancer, they usually do not lend specificity to the suggested relations.

Secular trends

Changes in cancer incidence or mortality over time have been related to fluctuations in dietary factors in an effort to explore possible diet–cancer associations. For example, Hems [3] assessed secular trends of dietary components and breast cancer mortality for the United Kingdom taking place between 1911 and 1971. Some of these findings are illustrated in Fig. 1. The trend for breast cancer mortality is seen to

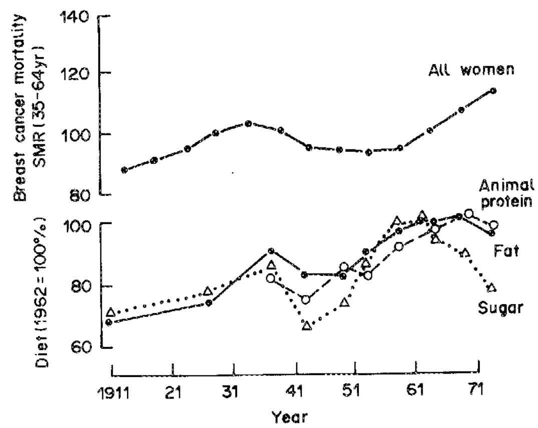

Fig. 1. Change with time of breast cancer mortality among women of England and Wales, and fat, animal protein and sugar in the diet (g/day) from 1911–15 to 1971–75 [3].

parallel those for dietary fat, animal protein, and sugar intake over the six decades shown. These data, coupled with supporting experimental data and several plausible mechanisms (e.g. enhanced estrogen metabolism or bile acid production), suggest a role for dietary fat in the etiology of breast cancer. The increase in breast cancer mortality beginning around 1960 apparently occurred 10–20 years after an increasing trend in dietary intake: the correlation between regional breast cancer rates and dietary fat was higher when intake of 10 years earlier was used (correlation coefficient $r = 0.6$), than when either the concurrent diet ($r = 0.4$) or that of two decades earlier ($r = 0.1$) was used. In contrast, international correlation analyses we have conducted using food availability data for fat and other nutrients, and 1973–1977 incidence rates for various cancers, show little or no effect of lag-time [4]. Correlating incidence data [5] from 1 year with either concurrent food data or those from approximately 12 years earlier [6] for 21 countries, we have observed for several cancer sites little difference in the correlations between the food data from either period and cancer incidence. For example, the Pearson correlation coefficient for breast, prostate, and colon cancers are 0.71, 0.56, and 0.79, respectively, when concurrent dietary fat data are used. For the food data from 12 years prior to the year of cancer incidence, the coefficients are 0.75, 0.59, and 0.79, respectively. Thus, while such studies cannot make inferences about the individual, they are supportive of associations such as between breast cancer and dietary fat.

Migrant studies

Descriptive studies of migrants have also contributed to our hypotheses concerning the effect of diet on cancer. Migrant populations are observed to undergo changes in exposure to suspected environmental risk factors (including diet) and health outcomes through time and space, while genetic factors may be considered relatively constant. Acculturation, the process by which traditional lifestyle is substituted over time for host country patterns, provides a necessary link between migration and dietary change. Determining the actual time of acculturation is not easily done, however, as the year of migration, as well as the age at migration, may independently affect the year of acculturation.

Several investigations have related the incidence of various neoplasms among Japanese migrants to their degree of acculturation to a Western lifestyle and diet. One such etiologic study of stomach cancer among male Japanese migrants in Hawaii by Haenszel *et al.* [7] found that migrants (but not their offspring) exhibited increased risk comparable to that of men in Japan, and that this elevated risk was associated with the consumption of specific Japanese foods such as pickled vegetables and salted fish, among others. In another study of migrants, Buell [8] describes the increasing incidence of breast cancer in successive generations of Japanese women in America, as compared to Japan (Table 1). He suggests that these changing rates may be attributable to dietary acculturation involving increased macronutrient intake, and reflected, at least in part, in increased height and weight during the growth period. However, data on specific dietary changes were not presented, so that the precise association with diet remains unclear in this study.

In contrast, Nomura *et al.* [9] compared the diet of Japanese men whose wives had developed breast cancer with the diets of other Japanese men who had participated in the Japan–Hawaii Cancer Study (the authors assumed that the diets of the husbands and wives were similar). Their results indicated that husbands of the breast cancer cases consumed a Western-style diet (more beef or other meat,

Table 1. Age-adjusted breast cancer incidence rates

Age	Japan	First generation	Second generation	U.S. whites
35–64	31.8	93.6	116.5	179.4
65–74	21.8	163.4	—	293.4

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beef or other meat,

cancer incidence rates

	Second generation	U.S. whites
	116.5	179.4
	—	293.4

butter/margarine/cheese, and corn), and ate less Japanese foods, than did men in the control group. Further examination of specific dietary changes occurring over time among migrant populations would be useful.

Anthropometry

Studying the nutritional component of human growth patterns and anthropometric variables offers an alternative assessment of changes in dietary factors over time. Anthropometry not only provides information regarding past nutritional history (particularly for macronutrients), but can evaluate age-specific effects of nutrition [10].

Anthropometric changes over time have been related to the increase in breast cancer frequency across successive cohorts of Japanese-American women [11]. This increase can be seen in the age-specific cancer rates for Japanese-American women in Los Angeles between 1972 and 1977. These rates are contrasted in Fig. 2 with the incidence for whites residing in the same area. Younger Japanese-American women have rates that are similar to those of U.S. whites, and are much higher than those of old Japanese-American women; the rates of the older Japanese-American women are similar to the low rates among women in Japan. Changes in cancer rates parellel growth patterns in that the younger cohort of Japanese-American women (born in 1955) evidenced greater growth and stature at age 17 years (158 cm; [12]) than the older (born in 1940) cohort (154 cm; [13]). These growth differences suggest that the younger (and taller) cohort had longer intake of a

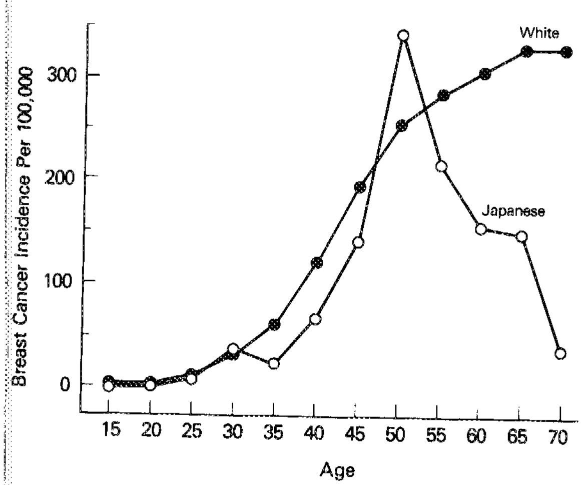

Fig. 2. Age-specific breast cancer incidence in Japanese vs white females, Los Angeles, U.S., 1972–1977 [5].

more Western diet which may have contributed to their increased incidence of breast cancer.

Given that growth is a function of dietary intake, international correlations between height or other anthropometric measures at different ages and cancer incidence or mortality can provide additional information about the general impact of diet, particularly over-nutrition, on breast and other cancers. We studied the relationships between age-specific anthropometric measurements [14], and breast cancer incidence [5] and mortality [15] rates in 34 populations around the world. Table 2 shows the correlation between breast cancer mortality and age-specific stature, weight and biacromial diameter. The correlation between breast cancer and each of these anthropometric variables increases with age across childhood and adolescence, and is highest for the oldest age groups. Similar results were obtained for breast cancer incidence [16]. Since dietary differences across countries are better reflected in growth differences at later rather than earlier ages, the fact that these correlations with breast cancer are stronger for later ages offers further support for the connection between diet and cancer.

Timing of dietary exposure

Time-related factors can also lend greater specificity to the nature of exposure (in this case diet), and allow more precise delineation of the association between diet and cancer than do descriptive studies. These parameters include: (1) age at exposure, (2) the duration of exposure, and (3) the time from exposure to tumor or cancer outcome. Unfortunately, few data are currently available from human studies which shed light on these issues with regard to diet–cancer associations. Laboratory experi-

Table 2. Cross-national correlation of age-specific anthropometric measures with age-adjusted breast cancer mortality

Age	Stature	Weight	Biacromial width
6	0.48	0.48	0.30
7	0.38	0.39	0.29
8	0.56	0.40	0.44
9	0.56	0.42	0.40
10	0.53	0.37	0.44
11	0.45	0.37	0.27
12	0.57	0.42	0.31
13	0.65	0.43	0.32
14	0.62	0.50	0.41
15	0.75	0.58	0.47
16	0.76	0.69	0.68
17	0.74	0.68	0.78
18	0.72	0.75	0.71

ments, however, have contributed to our knowledge in this area.

For example, in a series of studies involving comprehensive monitoring of diet, body size, and tumorigenesis in rats, Ross *et al.* [17] observed quantitative, time-dependent relationships between nutrition, growth, body size, and neoplasia. Both the age at various dietary exposures and the duration of those intake patterns were found to be highly predictive of subsequent tumorigenesis. Specifically, these investigators demonstrated that increased tumor incidence in animals was associated with: (1) a rapid growth rate during early postnatal life, (2) high absolute protein intake after weaning, (3) high efficiency of converting consumed food into body mass at the time of puberty, (4) high protein intake relative to body weight in early adulthood, and (5) high levels of food intake during adulthood.

Numerous experiments such as those of Verma *et al.* [18] and Tannenbaum and Silverstone [19] involve micronutrient supplementation (e.g. vitamin A derivatives) or dietary manipulation (e.g. fat or total calorie restriction) at various ages or periods of carcinogenesis. Although generalizations to humans from animal experiments must be made cautiously, these and similar studies suggest that chemopreventative agents or dietary modification in humans may have anti-carcinogenic effects, and that the timing of such interventions may be important. These investigations have shown, for example, that dietary factors can operate during the promotion stage of carcinogenesis, long after initiation has occurred [18, 20]. Thus, laboratory models afford unique opportunities to generate hypotheses which can be further tested through epidemiologic research.

RESEARCH DESIGN ISSUES

Time-related factors have important implications for the design of diet and cancer studies in humans. Four research aspects which require the attention of investigators include: (1) the evaluation of *critical etiologic periods*, (2) methods of *dietary assessment*, (3) utilization of *biologic indicators* of nutritional status, and (4) the effects of *secular trends*.

Critical etiologic periods

Although seldom addressed, each of the time-related factors of age, duration, and the time from exposure to cancer endpoints, should be considered when planning human diet–cancer research. In addition, hypotheses concerning multistage carcinogenesis in humans and the effects of diet on that process may suggest which periods of exposure should be investigated. For example, if dietary fat is believed to exhibit both early and late stage effects on breast carcinogenesis in animals [19, 21] and in humans [22], then case–control and cohort studies of this cancer should attempt to collect data for both early and late exposures. In prospective studies specifically, the time of data collection and the hypotheses concerning duration of exposure and latency of its effect will determine how long the investigators wait for study endpoints.

With regard to chemoprevention trials, time factors relating to the intervention are critical to study design. The primary intervention in this case is nutrient supplementation or dietary modification in a controlled, randomized fashion. Generally, agents believed to be effective in later stages of carcinogenesis are being employed in adult study populations [23]. Nutritional manipulation having primarily early-stage effects would necessitate the use of younger study populations for much longer periods in order to adequately test the efficacy of the intervention. Decisions must be made regarding the appropriate age and duration of intake for study participants, the lag-time of effect, and the pre-clinical latency period of the cancer, in order to exclude, or analyze separately, cancers present at the start of the study. Also, age-dependent competing causes of illness or death should be considered, since a large number of non-cancer deaths occurring among subjects can impede subsequent interpretation of cancer endpoints.

Dietary assessment

Epidemiologic studies in this area are hampered by difficulties in accurately assessing dietary intake. The several methods of assessing current diet that have been developed differ, in part, with respect to the time period over which intake is measured. The 24-hour recall, for example, includes all foods eaten over the previous day, while the food frequency instrument is designed to elicit average consumption of various foods over a longer period (e.g. 1 year). Block [24] has reviewed advantages and disadvantages of the various methods of relevance to current epidemiologic research. A particular time-related problem with the 24-hour recall method is the marked intra-individual variation in micronutrient consumption. Day-to-day variation can lead to severe dietary exposure misclassification when comparisons are being made among individuals. Liu *et al.* [25] and Sempos *et al.* [26] have examined this problem and have estimated for several micronutrients the number of 24-hour dietary recalls necessary to reduce misclassification to a specified level.

As difficult as it is to assess current dietary intake, it is more problematic to obtain reliable information on what a person ate in the distant past, especially in childhood and adolescence. However, because of the long period between the initiation of the carcinogenic process and its clinical manifestation, what people ate in the past may be as relevant to the diet–cancer connection as what they are eating now or during the previous few years. Earlier studies [27, 28] concluded that dietary information from the distant past tended to be unreliable, and, in particular, that estimates of past diet were biased by current intake. A recent study by Byers *et al.* [29], though, suggests that recollection of dietary practices from the distant past gave a better estimate of originally recorded dietary data than did the assessment of current practices, although the biased recollection of past dietary practices by the current diet remained a problem [24]. Given the potentially important influence of early diet on the risk of cancer, further research in this area is warranted. Re-interviews of subjects from prospective studies on whom earlier dietary data are available may be helpful in this regard [30]. Investigations of dietary recall in persons who spent early years in institutions such as schools or convents may also be instructive. Investigators may also obtain current dietary data from study participants and obtain information about past diet from the parents of participants, where available.

Biologic indicators

Since collection of valid early dietary intake data is constrained by a number of methodologic difficulties, the use of alternative measures of diet and nutrition becomes imperative. Blood nutrient levels offer such measures of nutritional status, which have been widely explored in diet–cancer studies. For example, a prospective study by Kark *et al.* [31] demonstrated that persons developing cancer had significantly lower serum vitamin A (i.e. retinol) levels at least 12 months before diagnosis than did persons remaining free from cancer (41.3 vs 46.9 μg/100 ml). Assessing vitamin A stability at -20°C, and that during periods of freeze–thaw and exposure to light (simulating conditions which may have occurred during the 14-year follow-up period), the authors showed no degradation of samples tested. While these and other investigators excluded cancers which developed soon (e.g. 1 year) after serum collection in an effort to minimize the effects of disease on nutrition, others specifically evaluate serum levels from cases which develop at different times throughout the surveillance period [32]. Thus, while the effects of cancer on such parameters can complicate the interpretation of case–control studies which obtain blood from known cases, prospective collection of appropriately stored blood samples may offer more meaningful tests for hypotheses.

Other useful nutritional markers include tissue samples such as toenails, which can be analyzed for selenium or other materials, and adipose tissue (reflecting dietary fatty acid composition), which may offer assessment of more distant nutritional status advantageous in various research settings. Also, as discussed earlier, anthropometry offers valid estimates of childhood, adolescent, or adult intake of important macronutrients by measuring parameters such as height, weight or skinfold thickness in adults which are enduring indicators of dietary intake [10].

Secular trends

Trends in diet and other variables should also be considered in the design of prospective studies and clinical trials concerned with diet and cancer, since secular trends can affect the results of these investigations. For example, the U.S. food supply has undergone changes since the beginning of this century, including increases in animal protein, total fat, cholesterol, vitamins A and C, as well as some of the B vitamins [33]. In contrast, consumption of crude fiber and carbohydrates has decreased, especially that from cereal products and potatoes. In addition, the use of vitamin and/or mineral supplements among adults 55–64 years old has increased in the U.S. from 34% in 1971, to 40% in 1980 [34]. Observations such as these should be considered when planning study sample size, subject recruitment, and other aspects of study design.

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